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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/528,691	09/21/2005	Gunnar Leo Karup	Q86966	4613

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SUGHRUE MION, PLLC
2100 PENNSYLVANIA AVENUE, N.W.
SUITE 800
WASHINGTON, DC 20037

EXAMINER	
CHANG, CELIA C	

ART UNIT	PAPER NUMBER
1625	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/528,691	KARUP ET AL.	
	Examiner	Art Unit	
	Celia Chang	1625	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 November 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) *1-3,5-10 and 13-20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *4, 11-12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's election without traverse of group III, claims 4, 11-12 reading on claim 4, in the reply filed on Nov. 3, 2008 is acknowledged.

Claim 4, and 11-12 reading on claim 4 are prosecuted. Claims 1-3, 5-10, 13-20 and the remaining subject matter of claims 11-12 are withdrawn from consideration.

2. Claim 4 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

It is very confusing as to what is being claimed. Please note that each acid addition salt is a different chemical compound and each solvate or hydrate is an independent and different chemical identify (see Seddon). It is very confusing as how many compounds are being claimed.

In addition, for racemates, there is the crystal of L-raloxifene lactate and D-raloxifene lactate in racemic mixture which will be physical mixing of a D-crystal and a L-crystal. Or it could be a racemic crystal of one D-raloxifene lactate and one L-raloxifene lactate. The two kinds of racemic crystal are distinct and different. It is understood by one having ordinary skill in the crystal art that racemic crystals are well known to be either (i) made of physical mixture of the R-crystal and S-crystal (homochiral crystals) which are separable by mechanical means (see Fasel et al. and Yokota et al.) ; or (ii) made of racemate unit, i.e 1-R and 1-S pair or less ordered ratio (heterochial crystals, the unit cells are made of both enantiomer, such as ibuprofen, see Zhang et al). There is no clarity as to what does the d-space or 2θ are drawn to, mixture of homochrial crystal? Or heterochiral crystal of paired R- and S- in the unit cell.

3. Claim 4 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

It is understood by one having ordinary skill in the crystal art that racemic crystals are well known to be either (i) made of physical mixture of the R-crystal and S-crystal (homochiral crystals) which are separable by mechanical means (see Fasel et al. and Yokota et al.) ; or (ii) made of racemate unit, i.e 1-R and 1-S pair or less ordered ratio (heterochial crystals, the unit cells are made of both enantiomer, such as ibuprofen, see Zhang et al). The claimed DL raloxifene lactate can only be one or the other. The specification provided no support that the d-space or 2θ of claim 4 are drawn to, mixture of homochrial crystal? Or heterochiral crystal of paired R- and S- in the unit cell.

4. Claims 11-12 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The standard for determining whether the specification meets the enablement requirement was cast in the Supreme Court decision of *Mineral Separation v. Hyde*, 242 U.S. 261, 270 (1916), where the Supreme Court looked to whether the experimentation needed to practice an invention was undue or unreasonable. *Id.* An invention must be described so that any person skilled in the art can make and use the invention without undue experimentation. *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988). As stated in the MPEP 2164.01(a) "There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue". The analysis must consider all the evidence related to each of these factors, and any conclusion of nonenablement must be based on the evidence as a whole. *Id.* at 740, *Id.* at 1407. The factors to be considered herein are those set forth as the In re Wands, 8 USPQ 2nd 1400 (1988) decision.

The analysis is applied to the instant case.

Nature of invention

The claims are drawn to a composition having the particular raloxifene DL-lactate hemihydrate having the D-space or 2θ properties, i.e. a specific crystalline form.

The state of the art and predictability

Per ponderous of factual evidence in "drugs" indicated that the temperature and pressure of pharmaceutical composition processing, such as tableting *would* cause transformation of "forms". See :

Muzaffar et al. p.60 "At any one temperature and pressure only one crystal form of a drug is stable and any other polymorph existing under these conditions will convert to the stable form …." And p.63-65 (a)-(h) pharmaceutical preparing processes affect polymorphism;

Jain et al. p.322-326, manufacturing processes that affect polymorphs ;

Doelker et al. abstract, "One may also observe changes in technology or pharmaceutical properties that are due to polymorphic environmental conditions undergone by the product or the dosage form"

Doelker et al. abstract "…a given drug, although chem. well defined, may exhibits quite different behavior. Process conditions (*grinding, tableting, granulations, drying)* may also affect secondary properties of the drug, such as compactibility, wetttability, soly, dissoln, rate, bioavailability and even pharmacol. activity."

Otsuke et al. p.852 « …in formulation studies and the method preparing CBZ has been shown to affect the drug's pharmaceutical properties through the polymorphic *phase transformation* of the bulk CBZ powder during the manufacturing process"

The amount of guidance and working examples

On pages 6-7, description of pharmaceutical composition using conventional carrier were disclosed, i.e. acidic solutions comprising sodium chloride (see p.6 line 9). In addition, conventional procedure for pharmaceutical formulation including wet processing and dispersion. Nowhere in the specification was a composition of raloxifene DL lactate hemihydrate which is defined explicitly to have all the properties with X-ray d-space/2θ etc., that is the *composition* containing the same X-ray diffraction pattern essentially as shown in claim 4. Nowhere in the specification a *composition* of this limitation of the claim was made.

In view of the per ponderous of evidence as delineated supra, it is evidenced that crystalline drug does not *automatically* keeps its crystalline form in the pharmaceutical composition, thus, *absent of any description or enablement* from the specification, enablement for the "claimed" composition is lacking.

The above per ponderous of evidence using conventional tableting/granulating material will result in not maintaining forms will also apply even if limiting the composition to solid formulations. Specifically the field of solid pharmaceutical excipient art indicated that such processing is more an art then science (see Lanz) and it is difficult to apply standard techniques to identify and predict the transformations [of solid material] (see CMU para bridging p.1-2). The specification therefore, did not provide the required guidance of what excipients and how a composition is made which maintains raloxifene DL lactate with the d-space or 2θ.

5. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Celia Chang, Ph. D. whose telephone number is 571-272-0679. The examiner can normally be reached on Monday through Thursday from 8:30 am to 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet L. Andres, Ph. D., can be reached on 571-272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

OACS/Chang
Jan. 12, 2009

/Celia Chang/
Primary Examiner
Art Unit 1625